High altitude journeys and flights are associated with an increased risk of flares in inflammatory bowel disease patients

Vavricka, Stephan R ; Rogler, Gerhard ; Maetzler, Sandra ; Misselwitz, Benjamin ; Safroneeva, Ekaterina ; Frei, Pascal ; Manser, Christine N ; Biedermann, Luc ; Fried, Michael ; Higgins, Peter ; Wojtal, Kacper A ; Schoepfer, Alain M

Abstract: BACKGROUND AND AIMS: Hypoxia can induce inflammation in the gastrointestinal tract. However, the impact of hypoxia on the course of inflammatory bowel disease (IBD) is poorly understood. We aimed to evaluate whether flights and/or journeys to regions lying at an altitude of >2000m above the sea level are associated with flare-ups within 4weeks of the trip. METHODS: IBD patients with at least one flare-up during a 12-month observation period were compared to a group of patients in remission. Both groups completed a questionnaire. RESULTS: A total of 103 IBD patients were included (43 with Crohn's disease (CD): mean age 39.3±14.6years; 60 with ulcerative colitis (UC): mean age 40.4±15.1years). Fifty-two patients with flare-ups were matched to 51 patients in remission. IBD patients experiencing flare-ups had more frequently undertaken flights and/or journeys to regions >2000m above sea level within four weeks of the flare-up when compared to patients in remission (21/52 [40.4%] vs. 8/51 [15.7%], p=0.005). CONCLUSIONS: Journeys to high altitude regions and/or flights are a risk factor for IBD flare-ups occurring within 4weeks of travel.

DOI: https://doi.org/10.1016/j.crohns.2013.07.011

Submission for *Journal of Crohn's and Colitis, vs* 20130403

High Altitude Journeys And Flights Are Associated With an Increased Risk Of Flares In Inflammatory Bowel Disease Patients

Stephan R. Vavricka[1,2], MD, Gerhard Rogler[2], MD PhD, Sandra Maetzler[2], MS, Benjamin Misselwitz[2], MD, Ekaterina Safroneeva[3], PhD, Pascal Frei[2], MD PhD, Christine N. Manser[2], MD, Luc Biedermann[2], MD, Peter Higgins, MD PhD MSc,[5] Kacper A. Wojtal[2], PhD, Alain M. Schoepfer[4], MD

1 Division of Gastroenterology and Hepatology, Stadtspital Triemli, Zurich, Switzerland

2 Division of Gastroenterology and Hepatology, University Hospital Zurich, Zurich, Switzerland

3 Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland

4 Division of Gastroenterology and Hepatology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

5 Division of Gastroenterology, University of Michigan, Ann Arbor, MI, USA

Short title: Impact of flights and altitude stays on activity in IBD

Correspondence address:

Stephan R. Vavricka, MD, PD

Division of Gastroenterology and Hepatology

Stadtspital Triemli

8063 Zurich

Switzerland

E-mail: stephan.vavricka@usz.ch

Tel: +41 44 466 13 17

Fax: +41 44 466 29 05

Or

Alain M. Schoepfer, MD, PD+MER1

Division of Gastroenterology and Hepatology

Centre Hospitalier Universitaire Vaudois / CHUV

Rue de Bugnon 44

1012 Lausanne, Switzerland

Email: alain.schoepfer@chuv.ch

Tel +41 21 310 7158

Fax +41 21 314 47 18

Disclaimers for all authors: The authors have no conflict of interest or financial interests related to the manuscript to disclose.

Writing assistance: none.

ABSTRACT

Background and aims: Hypoxia can induce inflammation in the gastrointestinal tract. However, the impact of hypoxia on the course of inflammatory bowel disease (IBD) is poorly understood. We aimed to evaluate whether flights and/or journeys to regions lying at an altitude of > 2,000 m above the sea level are associated with flare-ups within 4 weeks of the trip.

Methods: IBD patients with at least one flare-up during a 12-month observation period were compared to a group of patients in remission. Both groups completed a questionnaire.

Results: A total of 103 IBD patients were included (43 with Crohn's disease (CD): mean age 39.3 ± 14.6 years; 60 with ulcerative colitis (UC): mean age 40.4 ± 15.1 years). Fifty-two patients with flare-ups were matched to 51 patients in remission. IBD patients experiencing flare-ups had more frequently undertaken flights and/or journeys to regions > 2,000 m above sea level within four weeks of the flare-up when compared to patients in remission (21/52 [40.4 %] *vs.* 8/51 [15.7 %], p = 0.005). **Conclusions:** Journeys to high altitude regions and/or flights are a risk factor for IBD flare-ups occurring within 4 weeks of travel.

245 words

Key words: Crohn’s disease, ulcerative colitis, inflammatory bowel disease, hypoxia, hypoxic stress

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic, often debilitating intestinal disorder.[1,2,3] The etiology of IBD has not yet been fully elucidated; however, results of multiple studies point to a role of dysregulated innate and adaptive immune responses to intestinal bacteria.[4] Over the last few years, several studies have demonstrated that hypoxia can induce inflammation. Plasma levels of several inflammatory markers, such as interleukin-6, interleukin-1 receptor antagonist, and C-reactive protein, were found to be increased in healthy volunteers spending 68 hours at an elevation of 3,400 m above the sea level.[5] In murine models, exposure to normobaric hypoxia leads to tissue accumulation of polymorphonuclear neutrophils, increased serum levels of pro-inflammatory cytokines, and vascular leakage.[6,7,8,9,10] Hypoxia is a hallmark of many disease states and is known as a potent inflammatory stimulus. For example, ischemia in organ grafts increases the risk of inflammation in the graft with consecutive graft failure or rejection.[11] While hypoxia may lead to inflammation, inflammation can also lead to hypoxia in the tissue *via* different mechanisms, such as edema, vasoconstriction or production of reactive oxygen species triggering local oxygen depletion.[12] A steep oxygen concentration gradient, a consequence of the close proximity of the richly perfused oxygen bed to the anoxic bowel lumen, contributes to the unique oxygenation profile of the gut. Several studies have examined the role of hypoxia in mucosal tissue damage in IBD and shown that surgical specimens taken from patients with active CD and UC were found to contain elevated levels of hypoxia-inducible factors (HIF)-1α and HIF-2α.[13,14] These two factors trigger the expression of genes that are responsible for the maintenance of intestinal epithelial barrier function.[13,14] Furthermore, NF-κB also appears to play a role in response to stress, such as hypoxia, as activation of NF-κB in intestinal epithelial cells in response to gut ischemia-reperfusion in mice leads to increase in the production of proinflammatory cytokine tumor necrosis factor (TNF) and simultaneous attenuation of intestinal epithelial apoptosis.[15]

The fraction of oxygen in the air is 21 %, and barometric pressure at sea level is approximately 760 mm Hg. During airplane flights, the oxygen partial pressure in the cabin decreases, which leads to a reduction in the percentage of oxygen-saturated hemoglobin in the blood.[16] International laws demand that the cabin pressure must not be lower than the one measured at 8,000 ft (2,438 m; barometric pressure is 564 mm Hg).[17] A study evaluating the cabin pressure during 240 flights revealed that the cabin pressure ranged between the one detected at 5,000 ft (1,524 m; barometric pressure is 632 mm Hg) to that measured at 8,000 ft with a mean value corresponding to a pressure measured at 6,214 ft (1,894 m; barometric pressure is 604 mm Hg).[18] Breathing at 8,000 ft or at 5,000 ft is equivalent to breathing a hypoxic mixture with an oxygen fraction of 15.1 % or 17.1 % at sea level, respectively. Healthy subjects exposed to a hypoxic mixture of gases with 15.1 % or 17.1 % oxygen had a mean arterial oxygen pressure of 53 or 64 mm Hg (normal values 65 – 100 mm Hg) and mean arterial oxygen saturation of 85 % or 91 %, respectively.[19] While such decreases of arterial oxygen saturation are tolerated well by healthy subjects, this hypobaric hypoxia during aircraft travel may cause difficulties for patients with pulmonary disease.[16] Clinical data evaluating a potential impact of hypobaric hypoxia on disease activity in IBD is currently lacking. Therefore, we evaluated whether reduced oxygen partial pressure during aircraft travel and/or journeys to regions lying at an altitude of > 2,000 m above the sea level is associated with changes in clinical disease activity in four weeks following the trip.

MATERIALS AND METHODS

Patients

In this study, a questionnaire-based survey was conducted. IBD patients from in- and outpatient clinics of three Swiss tertiary hospitals (Triemli Zurich, University Hospital Zurich, and Centre Hospitalier Universitaire Vaudois) were recruited. The study was conducted as a project of the Swiss Inflammatory Bowel Disease Cohort Study and was approved by the Ethics Committees (SNSF 33CSC0_134274).[20] Prior to inclusion into the study, written informed consent was obtained from all patients.

Methods

For the purposes of the survey, IBD patients with at least one flare-up episode in the observation period from September 1st, 2010 to August 31st, 2011 were compared to IBD patients, who were in clinical remission during the same observation period. Data were obtained by the means of a structured questionnaire and review of medical charts. The questionnaire contained items addressing the following topics: demographics, medical history, medication history and the history of aircraft travel and/or high-altitude journeys (> 2,000 m above sea level), the duration of the trip(s) (in hours), date and flight destination, as well as details on travel habits within 4 weeks of the flare. CD patients were categorized into the groups with different disease location based on Montréal classification, where L1 corresponds to disease in the terminal ileum, L2 corresponds to disease in the colon, L3 corresponds to ileocolonic disease, and L4 corresponds to isolated disease in the upper gastrointestinal tract.[21] UC patients were categorized into the groups with different disease location according the Montréal classification, where E1 corresponds to rectal disease, E2 corresponds to left-sided colitis, and E3 corresponds to an extensive colitis.

Inclusion criteria for enrollment of CD and UC patients with flare-up episode(s) into this study were as follows: age 18 - 80 years, at least one flare-up episode in the observation period between September 1st, 2010 and August 31st, 2011. It was mandatory that the occurrence of a flare-up episode as reported by the patient was verified by a physician in the course of a clinical examination. Furthermore, in order to attribute a flare-up episode to IBD, an infectious etiology had to be excluded. For this reason, microbiological workup of fecal samples for known infectious agents, such as *Salmonella*, *Shigella*, *Campylobacter* spp., test for presence of *Clostridium difficile* toxin in feces, examination of 3 different fecal samples for parasites, and evaluation of biopsies for cytomegalovirus were carried out. No routine tests for other viral intestinal infections were performed. Inclusion criteria for enrollment of CD and UC patients in clinical remission into the study were as follows: age 18 - 80 years, maintenance of clinical remission during the observation period between September 1st, 2010 and August 31st, 2011. Exclusion criteria for a group with flare-up episode(s) and for a group in remission were as follows: perianal Crohn's disease, positive results of microbiological workup of fecal samples for known infectious agents during a flare-up episode, and any cardio-pulmonary condition affecting oxygen hemoglobin saturation, such as chronic obstructive pulmonary disease.

Definitions

Clinical activity in CD patients was assessed using the Harvey Bradshaw Index (HBI).[22] In 2006, using regression modeling, Best *et al.* reported that a one-point increase in a value of HBI corresponds to a 27-point increase in the value of CDAI.[23] For the purposes of this manuscript, the following definitions were applied: a value of HBI from 0 to 4 points indicates clinical remission (corresponds to a mean ± SD CDAI values of 26 ± 26 to 134 ± 39, respectively); a value of HBI from 5 to 7 points indicates mild disease (corresponds to a mean ± SD CDAI values of 161 ± 42 to 216 ± 49, respectively); a value of HBI from 8 to 15 indicates moderate disease (corresponds to a mean ± SD CDAI values of 243 ± 52 to 432 ±

75, respectively); and a value of HBI ≥ 16 indicates severe disease (corresponds to a mean ± SD CDAI value of ≥ 459 ± 78). A flare-up episode in CD patients was defined as a rise in HBI value of ≥ 4 points, which corresponds to a CDAI increase of ≥ 108 points.

Clinical activity in UC patients was assessed using the Rachmilewitz Index, which ranges from 0 to 29 points.[24] A value from 0 to 4 points indicates clinical remission; a value from 5 to 10 points corresponds to mild activity; a value from 11 to 17 indicates moderate activity; and a value of ≥ 18 points indicates highly active disease.[25] A flare-up in UC patients was defined as an increase in the Rachmilewitz Index value of ≥ 5 points.

Patients with clinical IBD flare-up(s) underwent clinical, endoscopic and laboratory examinations (see inclusion and exclusion criteria above). Only those patients with an increase in clinical activity attributed to IBD were included into the study.

Statistical analysis

Data from questionnaires were entered into EpiData version 1.1.2. All statistical analyses were performed with the statistical program STATA® (version 12, College Station, Texas, USA). *A priori* power analysis revealed that a sample size of 76 patients (38 patients for the group experiencing flare-up episode(s) and 38 patients for the group in remission) would have 90 % power to detect a difference in the rate of trips with the aircraft and/or to regions lying at an altitude of > 2,000 m above the sea level between these two groups. We expected a yearly rate of 20 trips by aircraft and/or to regions lying at an altitude of > 2,000 m above the sea level for the group experiencing flare-up episode(s) (standard deviation = 8) and a yearly rate of 15 trips for the group in remission (standard deviation = 5). Data distribution was analyzed using Normal-QQ-Plots. Results of quantitative data are presented as either mean ± SD and range (for parametric data) or median plus interquartile range (IQR) (for non-parametric data). Categorical data were summarized as the percentage of

the group total. Differences in quantitative data distributions were assessed by the Student's *t*-test (for parametric data) and by the Wilcoxon rank-sum test (in case of non-parametric data). The Kruskal-Wallis test was used for comparison of more than 2 independent samples. A *p*-value of < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

One hundred forty two IBD patients were screened. Of these, 103 (72.5 %) patients were included in the study. Forty-three patients had Crohn's disease (CD) (mean age 39.3 ± 14.6 years old), and 60 patients suffered from ulcerative colitis (UC) (mean age 40.4 ± 15.1 years old). Thirty nine patients were excluded for the following reasons: a flare-up episode was not confirmed by a physician or a definition of flare-up episode was not met (24), presence of perianal CD (4), unwillingness to participate (3), presence of infectious agents, such as ameba (1), *Giardia lamblia* (2), *C. difficile* (1), *Campylobacter jejuni* (2), and presence of chronic obstructive pulmonary disease (2).

Fifty-two patients experiencing flare-up episodes were compared to 51 patients in clinical remission. The background demographic characteristics and disease characteristics of the two groups are shown in **Table 1**. No difference between the two groups regarding smoking habits and level of regular physical activity was detected. For the purposes of this study, regular physical activity was defined as at least two 30-minute sessions of workout per week. CD patients suffered from 1.5 ± 1.1 flare-up episodes and UC patients from 2 ± 1.8 flare-up episodes in the observation period. Details on flare-up episode duration, severity, and treatment strategies are shown in **Table 2**. No association between a season or a month of the year and a frequency of IBD flare-up episodes was observed (data not shown).

Medication history

The medication history of patients with flare-up episodes and patients in remission is presented in **Table 3**. Aminosalicylates, immunomodulators and anti-TNF drugs were prescribed at similar frequencies to CD and UC patients with and without flare-up episodes during the observation period. As expected, systemic steroids were significantly more

frequently taken by CD and UC patients experiencing flare-ups during the study period. NSAIDs and antibiotics were prescribed at similar frequencies to both groups of patients.

Mild hypoxic stress was more frequent in patients with flare-up episodes compared to controls

Mild hypoxic stress was defined as aircraft travel and/or journeys to regions lying at an altitude of > 2,000 m above the sea level. Details regarding the occurrence of mild hypoxic stress in the two groups during the observation period between September 1st, 2010 and August 31st, 2011 are presented in **Table 4**. Twenty one patients in the group experiencing flare-up episodes (n = 52) traveled by aircraft and/or journeyed to regions lying at an altitude of > 2,000 m above the sea level within 4 weeks of occurrence of the flare-up when compared to 8 patients in the IBD group that were in clinical remission (40.4 % *vs.* 15.7 %, p = 0.005). These findings are illustrated in **Figure 2**. When a comparison between subgroups of IBD patients was made, 8/21 CD patients who experienced flare-up episode(s) had travelled by airplane or to high altitude regions when compared to 2/22 CD patients in clinical remission (38.1 % *vs.* 9.1 %, p = 0.024). In UC patients experiencing flare-up episodes, a trend for more frequent aircraft travel and journeys to higher regions was observed (13/31 *vs.* 6/29, p = 0.077).

A detailed analysis of the frequency, duration, and destination of the flights is provided in **Table 5**. IBD patients experiencing flare-up episodes more frequently travelled by aircraft when compared to IBD patients in remission (14/52 *vs.* 5/51, p = 0.025). On average, IBD patients experiencing flare-up episodes traveled 6.2 ± 4.2 hours when compared to 4 ± 4.1 hours in the IBD group in remission (p = 0.368).

We also analyzed the frequency and destination of travel to regions lying at an altitude of > 2,000 m above sea level (**Table 6**). Overall, IBD patients experiencing flare-up episodes had more frequently traveled to regions lying at an altitude of > 2,000 m above the sea level

when compared to IBD patients in remission (13/52 *vs.* 4/51, p = 0.019). The Swiss Alps were the most common travel destination.

DISCUSSION

Our study is the first to demonstrate that aircraft travel and journeys to regions at an altitude of > 2,000 m above sea level are risk factors for flare-ups in IBD patients. During a one-year observation period, patients experiencing flare-up episodes were more likely to have traveled by aircraft and/or to have journeyed to regions lying at an altitude of > 2,000 m above the sea level within four weeks of occurrence of a flare when compared with IBD patients in remission. We believe that these data are of particular importance in an era when international travel has become increasingly common, and people more than ever tend to use air travel as a preferred mode of transportation.

In a retrospective study, Soonawala *et al.* interviewed 277 IBD patients that traveled abroad within five years prior to the interview date. Sixty-two percent of patients reported that IBD limited their choice of travel destinations.[26] Such restrictions are often self-imposed stemming from a fear of occurrence of disease flare-up episodes or concerns over other travel-related health hazards. Indeed, the present study demonstrates for the first time that IBD patients are at an increased risk of experiencing flares soon after flying or traveling to regions at an altitude of > 2,000 m above sea level. Despite the impact on patients' quality of life, there are hitherto no studies investigating the risk of developing IBD flares in patients undertaking flights or travelling to high-altitude regions. While the data on risk of travel for patients with IBD are scarce, Soonawala *et al.* documented that 19 % (54 of 227) of IBD patients had a self-reported exacerbation of IBD within two months of travel, and 24 % of patients attributed the exacerbation to the recent travel. It has to be taken into account that these findings are based on patient-reported outcomes over a 5-year time period, and systematic exclusion of infectious agents as a factor potentially responsible for the occurrence of a new flare-up episode was not carried out. Ben-Horin *et al.* performed a

retrospective, case-controlled study of 222 patients with IBD and 224 healthy individuals that took 523 and 576 trips, respectively.[27] The authors reported that IBD patients had a higher rate of illness in comparison to control patients, while traveling to industrialized countries, but not to developing or tropical regions.[28] These observations cannot be compared to the results of our study since evaluation of whether flights or journeys to regions lying at an altitude of > 2,000 m above the sea level also represent risk factors for IBD flare-ups was not performed. Of note, Ben-Horin *et al.* have reported that 16 % of IBD patients experienced flare-up episodes within 3 months of returning from trips, whereas 40.4 % of IBD patients described in our study reported on such episodes within 4 weeks of travel. Our inclusion of patients who not only traveled by airplane (which is equivalent to exposure to oxygen levels typically observed in regions lying at altitudes of 2,000 - 2,500 m above the sea level) but also might have visited regions lying at an altitude of > 2,000 m above the sea level may be the reason for the observed difference in the occurrence of flares. If data obtained from only those patients who undertook aircraft travel are analyzed, the fraction of patients (26.9 %) experiencing IBD flare-up episodes within the four weeks of the flight is comparable to that reported by Ben-Horin *et al.* and Soonawala *et al.* [27,28]

It is important to mention that the two including centers (Lausanne and Zurich) are located on comparable altitudes (Zurich 408 m above sea level and Lausanne 495 m above sea level) as the difference in altitude of place of residence may be important in the interpretation of our results. Our data demonstrate an association between aircraft travel/journeys to regions lying at an altitude of > 2,000 m above the sea level and occurrence of IBD flare-up episodes. Potential underlying mechanisms need to be further discussed. Tissue hypoxia is known to be associated with upregulation of hypoxia-inducible factor HIF-1α which in turn can upregulate inflammation. This suggests that pro-inflammatory signaling could increase the susceptibility to hypoxia in affected intestinal tissues of IBD patients. In a murine dextrane sulfate sodium (DSS)-induced acute colitis model, HIF-1α expression correlated with clinical symptoms severity and histologic

damage.[28] HIF-1α expression triggers transcription of many genes that ameliorate intestinal epithelial cell barrier function, including TNFα.[12] For example, it has been shown that intestinal epithelial cells can adapt to hypoxia and that the HIF system may play a role in this type of adaptation.[12] A randomized controlled trial in which IBD patients are exposed to hypoxic air by the means of a hypoxia altitude stimulation test (HAST) would provide better understanding of the link between hypoxia and occurrence of IBD flares. HAST was useful in evaluating the necessity of oxygen supplementation for patients with cardio-pulmonary limitations during air travel.[16] However, this type of study design may not be feasible for IBD patients due to ethical reasons in view of the results presented in this manuscript. One might hypothesize that increased clinical activity seen after colonoscopy in UC patients might be related to short-term hypoxia in sedated patients.[29] This study identified factors that put patients at greater risk of a post-procedure flare, including use of steroids, and those that reduced the risk, including long-term use of thiopurines.[30]

Our study has several strengths and limitations. To the best of our knowledge, this is the first study that systematically assessed aircraft travel and stays in regions at an altitude of > 2,000 m above the sea level as potential triggering factors for IBD flares. The data obtained from the group of patients that travelled by aircraft and those obtained from the group that stayed in a region lying at an altitude of > 2,000 m above the sea level were combined for analysis as hypoxic stress experienced by an individual in either of the situations is equivalent to a decrease in PaO2 to levels between 53 - 64 mm Hg. Inhalation of air under conditions of decreased PaO2 corresponds to inhalation of a hypoxic air mixture containing about 15 - 17 % of oxygen.[16] One of the strengths of the current study is the application of strict inclusion and exclusion criteria such as requiring confirmation each flare by a physician as well as thorough microbiologic work-up of each flare. In general, patients with unstable IBD are less likely to travel, which would tend to bias this study toward a null result, making the positive result found more remarkable. The retrospective design and relatively small size of the population, which included only patients from Switzerland, are limitations of this study.

In addition, while the results of this study suggest an association between aircraft travel/stays at regions lying at an altitude of > 2,000 m above the sea level and IBD flare-up episodes, additional confounding factors, such as travel-related stress or exposure to different microbes in food, could have also contributed to observations made in the study. To address these limitations, we are currently planning a larger study using a decompression chamber that allows evaluating the impact of hypoxic stress onto the organism. Furthermore, while mouse models suggest that hypoxia triggers HIF expression and TNFα activation, the exact mechanism of how mild hypoxic stress can trigger bowel inflammation in humans needs to be elucidated. Finally, despite the close matching between the patient characteristics in both groups, systematic differences between these groups cannot be excluded.

In summary, we found that IBD patients with recent flare-up episodes more frequently travelled by aircraft or journeyed to high altitude regions within four weeks of experiencing these episode(s) when compared to the group that remained in remission. We conclude that flights and stays at an altitude of > 2,000 m above the sea level are a risk factor for IBD flare-up episodes.

Acknowledgments:

Specific author contributions:

(1) study concept and design; (2) acquisition of data; (3) analysis and interpretation of data; (4) drafting of the manuscript; (5) critical revision of the manuscript for important intellectual content; (6) statistical analysis; (7) obtained funding; (8) technical or material support; (9) study supervision; (10) final approval of the manuscript

Stephan R. Vavricka: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10; Gerhard Rogler: 1, 2, 3, 5, 7, 8,10; Sandra Maetzler: 2, 3, 4, 5, 10; Benjamin Misselwitz: 2, 3, 4, 5, 8, 10; Ekaterina Safroneeva: 3, 4, 5, 6, 8, 10; Pascal Frei: 2, 3, 4, 5, 10; Christine N. Manser: 2, 3, 4, 5, 10; Luc Biedermann: 2, 3, 4, 5, 10; Kacper A. Wojtal: 1, 2, 3, 5, 6, 8, 10; Alain M. Schoepfer: 1, 2, 3, 4, 5, 6, 7, 8, 9,

10.

Grant support: This research was supported by grants from the Swiss National Science Foundation (SNSF) to SRV (Grant No. 320000-114009/3 and 32473B_135694/1), to GR (Grant No. 310030-120312), to AS (Grant No. 32003B_135665/1), and to the Swiss IBD Cohort (Grant No. 3347CO-108792), and research grants from Vifor Pharma Ltd. and the Center for Integrative Human Physiology of the University of Zurich to SRV and GR. This is an investigator-initiated study.

FIGURE LEGENDS

Figure 1:

Flight destinations in the group of patients with flare-ups (n=14, blue lines) and in the group of patients that were in remission (n=4, green lines).

Figure 2:

Altitude of stays > 2,000 m above the sea level in the group of patients with flare-ups (n=13) and in the group of patients that stayed in remission (n=4) during the observation period (the interval from September 1st, 2010 to August 31st, 2011). The number above the graft represents days of stay at this altitude.

Figure 3:

The frequency of aircraft or a high altitude travel (> 2, 000 m above the sea level) in the group of patients with flare-ups and in the group of patients that stayed in remission during the observation period (the interval from September 1st, 2010 to August 31st, 2011).

TABLES

Table 1:

Patient characteristics. Abbreviations: NA, not applicable; CD, Crohn's disease; UC, ulcerative colitis; SD, standard deviation. *Kruskal Wallis test.

Item	**Remission**	**Flare-up**	***p*-value**
Number of patients	51	52	NA
Diagnosis - CD - UC	 22 (51.2 %) 29 (48.3 %)	 21 (48.8 %) 31 (51.7 %)	 0.777
CD location	L1 4 (18.2 %) L2 6 (27.3 %) L3 11 (50.0 %) L4 1 (4.5 %)	L1 3 (14.3 %) L2 5 (23.8 %) L3 13 (61.9 %) L4 0	0.768*
UC location	E1 4 (13.7 %) E2 9 (31.0 %) E3 16 (55.3 %)	E1 3 (9.7 %) E2 12 (38.7 %) E3 16 (51.6 %)	0.806*
Gender, females	29 (51.8 %)	27 (48.2 %)	0.615
Age (mean ± SD)	40.2 ± 14.6	37.6 ± 13.4	0.731
Age in males (mean ± SD)	42.4 ± 13.3	38.2 ± 14.0	0.588
Age in females (mean ± SD)	38.5 ± 13.9	37.1 ± 13.1	0.852
Smoking status	2/51 (3.9 %)	4/52 (7.7 %)	0.414
Regular sports activities	18/51	20/52	0.739
Pregnancy	0	0	NA
Mean number of flare-ups/year	0	1.8 ± 1.7	< 0.001
Mean number of flare-ups in CD patients	0	1.5 ± 1.1	< 0.001
Mean number of flare-ups in UC patients	0	2.0 ± 1.8	< 0.001

Hier noch Einfügen Hb 13.0 13.4 ns

Table 2:

Characteristics of the flare-up episodes experienced during the interval from September 1st, 2010 to August 31st, 2011. Up to 3 flare-ups per patient were recorded. Non-parametric data are depicted as median and IQR (interquartile range). Abbreviations: NA, not applicable; CD, Crohn's disease; UC, ulcerative colitis; SD, standard deviation

Item	**Flare-up 1** **n = 52**	**Flare-up 2** **n = 7**	**Flare-up 3** **n = 2**
Flare duration in weeks (median, IQR)	5 [2-12]	4 [2-8]	5 [5-5]
Flare severity			
- mild	5 (9.6 %)	2 (28.6 %)	0
- moderate	23 (44.2 %)	4 (57.1 %)	1 (50%)
- severe	24 (46.2 %)	1 (14.3 %)	1 (50%)
Harvey-Bradshaw Index for CD patients (median, IQR)	13 [11-15]	11 [7-13]	6 [6-6]
Rachmilewitz Index for UC patients (median, IQR)	9 [5-11]	7 [6-10]	8 [8-8]
Type of surgery performed as a consequence of flare-up			
- bowel resection	2 (3.8%)	0	0
- abscess drainage	1 (1.9%)	0	0
- dilation	1 (1.9%)	0	0

Table 3:

Medication history in the group of patients with flare-ups and in the group of patients that were in remission during the observation period. Abbreviations: NA, not applicable; CD, Crohn's disease; UC, ulcerative colitis; SD, standard deviation.

Item	**Remission**	**Flare-up**	***p*-value**
Number of patients	51	52	NA
Medication in CD patients (n = 43)			
- Aminosalicylates	4/22 (18.2 %)	5/21 (23.8 %)	0.650
- Azathioprine / 6-MP	15/22 (68.2 %)	13/21 (61.9 %)	0.666
- Methotrexate	4/22 (18.2 %)	2/21 (9.5 %)	0.413
- Anti-TNF	6/22 (27.3 %)	8/21 (38.1 %)	0.449
- Systemic steroids	0	16/21 (76.2 %)	< 0.001
Medication in UC patients (n = 60)			
- Aminosalicylates	17/29 (58.6 %)	16/31 (51.6 %)	0.586
- Azathioprine / 6-MP	16/29 (55.2 %)	18/31 (58.1 %)	0.821
- Methotrexate	1/29 (3.4 %)	0	0.297
- Anti-TNF	4/29 (13.8 %)	7/31 (22.6 %)	0.379
- Systemic steroids	1/29 (3.4 %)	19/31 (61.3 %)	< 0.001
NSAID intake	7/51 (13.7 %)	10/52 (19.2 %)	0.452
NSAID intake one month prior to flare-up episode	2/51 (3.9 %)	4/52 (7.7 %)	0.414
Antibiotic intake one month prior to flare-up episode	2/51 (3.9 %)	4/52 (7.7 %)	0.414

Table 4:

Frequency of flights and/or stays at an altitude of > 2,000 m above the sea level in the group of patients with flare-ups and in the group of patients that were in remission during the interval from September 1st, 2010 to August 31st, 2011. Abbreviations: NA, not applicable; CD, Crohn's disease; UC, ulcerative colitis; SD, standard deviation.

Item	**Remission**	**Flare-up**	***p*-value**
Number of patients	51	52	NA
Flights and/or stay at an altitude of > 2,000 m above the sea level - all IBD patients	8/51 (15.7 %)	21/52 (40.4 %)	0.005
Flights and/or stay at an altitude of > 2,000 m above the sea level - CD patients	2/22 (9.1 %)	8/21 (38.1 %)	0.024
Flights and/or stay at an altitude of > 2,000 m above the sea level - UC patients	6/29 (20.7 %)	13/31 (41.9 %)	0.077
Flights and/or stay at an altitude of > 2,000 m above the sea level – males	6/22 (27.3 %)	13/25 (52.0 %)	0.085
Flights and/or stay at an altitude of > 2,000 m above the sea level – females	2/29 (6.9 %)	8/27 (29.6 %)	0.026

Table 5:

Flight frequency and duration in the group of patients with flare-ups and in the group of patients that were in remission during the observation period from1st, 2010 to August 31st, 2011. Abbreviations: NA, not applicable.

Item	**Remission**	**Flare-up**	***p*-value**
Number of patients	51	52	NA
Flight frequency - all IBD patients	5/51 (9.8 %)	14/52 (26.9 %)	0.025
Flight frequency - CD patients	2/22 (9.1 %)	5/21 (23.8 %)	0.191
Flight frequency - UC patients	3/29 (10.3 %)	9/31 (29.0 %)	0.071
Flight frequency – males	3/22 (13.6 %)	9/25 (36.0 %)	0.079
Flight frequency - females	2/29 (6.9 %)	5/27 (18.5 %)	0.189
Number of flights (mean ± SD)	1.75 ± 0.5	1.71 ± 0.5	0.896
Flight duration (hours, mean ± SD)	4 ± 4.1	6.2 ± 4.2	0.368

Table 6:

Frequency and location of stays at an altitude of > 2,000 m above the sea level in the group of patients with flare-ups and in the group of patients that stayed in remission during the observation period (the interval from September 1st, 2010 to August 31st, 2011).

Item	**Remission (n = 51)**	**Flare-up (n = 52)**	***p*-value**
Stays at an altitude of > 2,000 m above the sea level - all IBD patients	4/51 (7.8 %)	13/52 (25 %)	0.019
Stays at an altitude of > 2,000 m above the sea level - CD patients	0/22	3/21 (14.3 %)	0.066
Stays at an altitude of > 2,000 m above the sea level - UC patients	4/29 (13.8 %)	10/31 (32.3 %)	0.091

REFERENCES

[1] Peyrin-Biroulet L, CIeza A; Sandborn WJ, *et al*. Disability in inflammatory bowel diseases: developing ICF core sets for patients with inflammatory bowel diseases based on the international classification of functioning disability, and health. Inflam Bowel Dis 2010;16:15-22.
[2] Irvine EJ. Quality of life issues in patients with inflammatory bowel disease. AM J Gastroenterol 1997;92:18S-24S.
[3] Vavricka SR, Rogler G. Recent advances in the etiology and treatment of Crohn's disease. Minerva Gastroenterol Dietol 2010;56: 203-11.
[4] Vavricka SR, Rogler G. New insights into the pathogenesis of Crohn's disease: are they relevant for therapeutic options? Swiss Med Wkly 2009;139:527-34.
[5] Hartmann G, Tschöp M, Fischer R, *et al*. High altitude increases circulating interleukin-6, interleukin-1 receptor antagnoist and C-reactive protein. Cytokine 2000;12:246-52.
[6] Rosenberger P, Schwab JM, Mirakaj V, *et al*. Hypoxia-inducible factor-dependent induction of netrin-1 dampens inflammation caused by hypoxia. Nat Immunol 2009;10:195-202.
[7] Eckle T, Faigle M, Grenz A, *et al*. A2B adenosine receptor dampens hypoxia-induced vascular leak. Blood 2008;111:2024-35.
[8] Eltzschig HK, Ibla JC, Furuta GT, *et al.* Coordinated adenine nucleotide phosphohydrolysis and nucleoside signaling in posthypoxic endothelium: role of ectonucleotidases and adenosine A2B receptors. J Exp Med 2003;198:783-96.
[9] Thompson LF, Eltzschig HK, Ibla JC, *et al*. Crucial role for ecto-5-nucleotidase (CD73) in vascular leakage during hypoxia. J Exp Med 2004;200:1395-405.
[10] Eltzschig HK, Abdulla P, Hoffman E, *et al*. HIF-1-dependent repression of equilibrative nucleoside transporter (ENT) in hypoxia. J Exp Med 2005;202:1493-505.
[11] Kruger B, Krick S, Dhillon N, *et al.* Donor Toll-like receptor 4 contributes to ischemia and reperfusion injury following human kidney transplantation. Proc Natl Acad Sci U S A 2009;106:3390-5.
[12] Colgan SP, Taylor CT. Hypoxia: an alarm signal during intestinal inflammation. Nature Reviews Gastroenterol Hepatol 2010;7:281-7.
[13] Karhausen J, Furuta GT, Tomaszewski JE, *et al*. Epithelial hypoxia-inducible factor-1 is protective in murine experimental colitis. J Clin Invest 2004;114:1098-106.
[14] Giatromanolaki A, Sivridis E, Maltezos E, *et al*. Hypoxia inducible factor 1alpha and 2alpha overexpression in inflammatory bowel disease. J Clin Pathol 2003; 56:209-13.
[15] Chen LW, Egan L, Li ZW, *et al.* The two faces of IKK and NF-kappaB inhibition: prevention of systemic inflammation but increased local injury following intestinal ischemia reperfusion. Nat Med 2003;9:575-81.
[16] Tzani P, Pisi G, Aiello M, *et al.* Flying with respiratory disease. Respiration 2010;80:161-70. Review.
[17] Code of Federal Regulations: Title 14, Part 25.841. Washington, Government Printing Office, 1986.
[18] Cottrell JJ. Altitude exposures during aircraft flight. Chest 1988;93:81-4.
[19] British Thoracic Society Standards of Care Committee: managing passengers with respiratory disease planning air travel: British Thoracic Society recommendations. Thorax 2002;57:289-304.
[20] Pittet V, Juillerat P, Mottet C, *et al.* Cohort profile : the Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS). Int J Epidemiol 2009;38:922-31.
[21] Silverberg MS, Satsangi J, Ahmad T, *et al*. Toward an integrated clinical, molecular, and serological classification of inflammatory bowel disease: Report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol 2005;19(Suppl A): 5-36.

[22] Harvey RF, Bradshaw MJ. A simple index of Crohn's disease activity. Lancet 1980;1:514.
[23] Best WR. Predicting the Crohn's disease activity index from the Harvey-Bradshaw index. Inflamm Bowel Dis 2006;12:304-10.
[24] Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. Br Med J 1989;298:82-6.
[25] Schoepfer AM, Beglinger C, Straumann A, *et al*. Ulcerative colitis: correlation of the Rachmilewitz endoscopic activity index with fecal calprotectin, clinical activity, C-reactive protein, and blood leukocytes. Inflamm Bowel Dis 2009;15:1851-8.
[26] Soonawala D, van Eggermond AM, Fidder H, *et al*. Pretravel preparation and travel-related morbidity in patients with inflammatory bowel disease. Inflamm Bowel Dis 2012;18:2079-85.
[27] Ben-Horin S, Bujanover Y, Goldstein S, *et al*. Travel-associated health risks for patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2012;10:160-5.
[28] Shah YM, Ito S, Morimura K, *et al*. Hypoxia-inducible factor augments experimental colitis through an MIF-dependent inflammatory signaling cascade. Gastroenterology 2008;134:2036-48.
[29] Menees S, Higgins P, Korsnes S, *et al*. Does colonoscopy cause increased ulcerative colitis symptoms? Inflamm Bowel Dis 2007;13:12-8.